Clinical Impact of Custodiol Cardioplegic Solution on Patients Undergoing Complex Cardiac Surgery With Mild to Moderate Impairment of Left Ventricular Systolic Function

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Abstract

Background: The Bretschneider HTK solution is used widely for multiorgan preservation for transplantation, as well as a cardioplegic agent that allows single dose administration which is an attractive option for lengthy complex cardiac surgery. It was proved that it is simple to use, safe and practical. Moreover, it is considered to confer sufficient myocardial protection for more than 2 h of cardiac arrest. We undertook this descriptive study to analyze the performance of HTK solution in patients undergoing complex cardiac surgery with mild to moderate impairment of left ventricular systolic function. **Patients and methods:** A total of 50 patients underwent different complex cardiac surgery at national heart institute from January 2015 to November 2016 using single dose Custodiol cardioplegia as the primary and sole cardioplegic agent, their data was prospectively collected and their hospital outcome was analyzed as regards to ten study endpoints namely Prolonged ventilation, return to theatre for bleeding, renal failure, stroke, 30 days mortality, postoperative MI, need for inotropes, time on inotropes, ICU stay and hospital stay. Pre- and postoperative echocardiography was done to compare and evaluate the change of LV function using the parameters of End Systolic Dimension, End Diastolic Dimension, Fraction Shortening and Ejection Fraction of the left ventricle. **Results:** Half of the patients were males. Their age ranged between 16 – 65 years with a mean (standard deviation) of 47.46(11.10). preoperative ejection fraction ranged from 30 % to 49% with a mean (standard deviation) of 41.8 (6.32), the majority of them (64%) had NYHA class of 3 and half of them had CCS of 3. all patients were done electively. The most common procedure done was redo DVR 24% (12 patients) followed by Bentall operation 22%(11 patients). This is followed by CABG + MVR 7 patients (14%), then an equal number of 6 patients (12%) who underwent redo MVR post-infective endocarditis and CABG+ MVrep. The repair of tricuspid valve was done for 14 patients (28%) either with MVR or DVR. 4 patients (8%) had CABG +AVR for their combined lesions and another equal number of two patients (4%) underwent redo CABG and AVR + conduit (valve separate tube graft operation). prolonged ventilation occurred in 20% of the cases. An equal percentage of 6% of the patients had to return to the operative room and had postoperative MI. Renal failure occurred in 4% of the patients and as far as 30-day mortality is concerned, a similar 4% of patients died within this period. EF and FS were very similar when compared together (41.8 ± 6.32 %, 20.8 ± 2.35 % preoperatively compared to 41.92 ± 7.49%, 20.85 ± 3.25% postoperatively). P value was insignificant (0.937 and 0.929) respectively. **Conclusion:** A single dose of an HTK cardioplegic solution provides good myocardial protection in complex cardiac surgery with mild to moderate impairment of LV function and has a good immediate postoperative outcome.

Keywords: Cardiac surgery; Myocardial protection; Histidine-Tryptophan-ketoglutarate cardioplegic solution; Left Ventricular Systolic Function

Introduction

The best method for preserving cardiac muscle viability during cardiac surgery without harm to myocardial function deserves extensive work and research (Mehlhorn U, 1995). The Bretschneider HTK solution is used widely for multiorgan preservation for transplantation, as well as a cardioplegic agent that allows single dose administration (Arslan A, 2005). It was proved that Custodiol HTK solution is simple to use, safe and practical and administered as one single dose. Moreover, it is considered to confer sufficient myocardial protection for more than 2 hours of cardiac arrest (Gamal Z., 2014).

Custodiol is definitely attractive for cardiac surgeons as it is delivered as a single dose and can offer myocardial protection for up to three hours (Bretschneider HJ., 1980, Gebhard MM, 1984) hence facilitating a proper technical flow of complex surgical procedures without interruption. Examining the clinical performance of this particular solution in complex heart surgery and LV impairment had received a little attention. We therefore undertook this descriptive study to investigate this aspect.

Study endpoints

Our primary study endpoints were ten points of early postoperative events. Prolonged ventilation, return to theatre for bleeding, renal failure, stroke, 30-day mortality, postoperative MI, postoperative intra-aortic balloon pump (IABP) insertion and /or need for inotropes, time on inotropes, ICU stay and hospital stay.

MI was defined as at least two of the following: (1) CKMB of 100 μg/L or more and/or troponin I of 3.0 μg/L or more, (2) appearance of new postoperative Q waves on the EKG of more than 0.03 seconds, and (3) a new hypokinetic or akinetic area in the left or right ventricle by echocardiography. New renal failure was defined as at least two of the following: serum creatinine increased to > 0.2 mmol/l, doubling or greater increase in serum creatinine over the preoperative value and a new requirement for renal replacement therapy. Stroke was defined as any new permanent neurological deficit lasting more than 72 hours after cardiac surgery and was confirmed by computed tomography whenever possible. Prolonged ventilation is defined as more than 24hours ventilation. Low cardiac output syndrome was defined as the need for postoperative intraaortic balloon pump or inotropic support for longer than 30 minutes in the intensive care unit to maintain the systolic blood pressure greater than 90 mm Hg.

Surgical technique

Hemodynamic monitoring was carried out via an arterial line in the radial and/or femoral artery as well as urine output via a urinary catheter. Conventional general anesthesia was used in all patients. The surgical approach was via median sternotomy.

After aortic cross-clamping, the cardioplegic arrest was induced by giving patients 20 ml/kg of HTK cardioplegic solution (Custodiol; Koehler Chemi, Alsbach-Hδhnlein, Germany) once. Each liter contained 15 mmol/l sodium chloride,10 mmol/l potassium chloride, 18 mmol/l histidine hydrochloride, 180 mmol/l histidine, 4 mmol/l magnesium chloride, 2 mmol/l tryptophan, 30 mmol/l mannitol, 0.015 mmol/l calcium chloride, and 1 mmol/l potassium hydrogen 2-ketoglutarate (osmolarity 310 /kg, pH 7.02-7.20). The cardioplegic solution was administered at a temperature of 4-8°C in an antegrade fashion at an initial perfusion pressure of 80–100 mmHg. When the myocardium was at standstill, the perfusion pressure was maintained at 40–60 mmHg. the systemic temperature was lowered to 32°C.

Patients and methods

A total of 50 patients underwent different complex cardiac surgery at national heart institute from January 2015 to November 2016 using single-dose Custodiol cardioplegia as the primary and sole cardioplegic agent, their data was prospectively collected and their hospital outcome was analyzed as regards to ten study endpoints namely Prolonged ventilation, return to theatre for bleeding, renal failure, stroke, 30 days mortality, postoperative MI, need for inotropes, time on inotropes, ICU stay and hospital stay. Pre- and postoperative echocardiography was done to compare and evaluate the change of LV function using the parameters of End Systolic Dimension in cm, End Diastolic Dimension in cm, Fraction Shortening in percentage and Ejection Fraction of the left ventricle in percentage.

Table 1. demonstrates the preoperative and clinical criteria of the study group. Half of them males. Their age ranged between 16 – 65 years with a mean (standard deviation) of 47.46 (11.10). The incidence of DM and hypertension was similar in the study group (56%) and the minority was smokers (20%)and having COPD (10%). preoperative ejection fraction ranged from 30 % to 49% with a mean (standard deviation) of 41.8 (6.32), 19 patients (38%) had preoperative pulmonary hypertension. 15 patients (30%) experienced MI before their operation and as far as their clinical status was concerned, the majority of them (64%) had NYHA class of 3 and half of them had CCS of 3. all patients were done electively.

Table 2 shows the operative details of the study group. The most common procedure done was Redo DVR 24% (12 patients) followed by Bentall operation 22% (11 patients). This is followed by CABG + MVR 7 patients (14%), then an equal number of 6 patients (12%) who underwent redo MVR post-infective endocarditis and CABG+ MVrep. The repair of tricuspid valve was done for 14 patients (28%) either with MVR or DVR. 4 patients (8%) had CABG +AVR for their combined lesions and another equal number of two patients (4%) underwent redo CABG and AVR + conduit (valve separate tube graft operation). Cardiopulmonary bypass time ranged from 100 – 184 minutes with a mean (standard deviation) of 149.10 (33.43). Cross-clamp time ranged between 65 – 140 minutes with a mean (standard deviation) of 111.30(28.34) minutes and finally, operative time ranged between 195 – 315 minutes with a mean (standard deviation) of 242.50 (43.81).

Table 1. Demographic criteria of the study group

Sex	Females	25 (50.0%)
	Males	25 (50.0%)
Age (years)	Mean ± SD	47.46 ± 11.10
	Range	16 – 65
Smoking	No	40 (80.0%)
	Yes	10 (20.0%)
DM	No	28 (56.0%)
	Yes	22 (44.0%)
HTN	No	28 (56.0%)

	Yes	22 (44.0%)
COPD	No	45 (90.0%)
	Yes	5 (10.0%)
Dyslipidemia	No	28 (56.0%)
	Yes	22 (44.0%)
MI	No	35 (70.0%)
	Yes	15 (30.0%)
LVEF (%)	Mean ± SD	41.8 ± 6.32
	Range	30 – 49
Pul. HTN (mmHg)	No	31 (62.0%)
	Yes	19 (38.0%)
NYHA	1	2 (4.0%)
	2	9 (18.0%)
	3	32 (64.0%)
	4	7 (14.0%)
CCS	1	11 (22.0%)
	2	10 (20.0%)
	3	25 (50.0%)
	4	4 (8.0%)

DM, Diabetes mellitus; HTN, hypertension; COPD, Chronic obstructive pulmonary disease; MI, Myocardial infarction; LVEF, left ventricular Ejection fraction; Pul. HT, Pulmonary hypertension; NYHA, New York Heart Functional Association; CCS, Canadian chest pain score

Table 2. Operative data of the study group

Variable.	Number of patients	Percentage
Tricuspid repair	14	28.00%
Redo DVR	12	24.00%
Bentall	11	22.00%
CABG+MVR	7	14.00%
Redo MVR(ENDOCARDITIS)	6	12.00%
CABG + MVrep	6	12.00%
CABG + AVR	4	8.00%
Redo CABG	2	4.00%
AVR + supra CC	2	4.00%
	Range	Mean ± SD
CPBT (min)	100 – 184	149.10 ± 33.43
X clamp (min)	65 – 140	111.30 ± 28.34

Operative time (min)	195 – 315	242.50 ± 43.81

DVR, Double valve replacement; CABG, Coronary artery bypass grafting; MVR, mitral valve replacement; MVrep, mitral valve repair; AVR, Aortic valve replacement; supra CC, supra coronary conduit; CPBT, cardiopulmonary bypass time; X clamp: Cross clamp time.

Table 3. demonstrates early postoperative outcome, prolonged ventilation occurred in 20%of the cases. An equal percentage of 6% of the patients had to return to the operative room and had postoperative MI. Renal failure occurred in 4% of the patients and as far as 30-day mortality is concerned, a similar 4% of patients died within this period. One case had a Bentall procedure and experienced excessive postoperative medical bleeding returned to theatre for re-exploration. Postoperative consumption coagulopathy was diagnosed and in spite of giving the products required, yet the patient did not survive. The second mortality was due to postoperative MI and cardiogenic shock in a case of redo CABG. Only 2% of patients had a postoperative stroke. 84% of patients needed inotropes namely (noradrenaline 52%, adrenaline 44%, levosimendan 30%, 24% and balloon 12%). These inotropes lasted from 12 – 60 hours with a mean (standard deviation) of 22.69 (13.3). their stay in the ICU ranged from 48-96 hours with a mean (standard deviation) of 73.2 (15.12). Their hospital stay ranged from 8 – 12 days with a mean (standard deviation) of 10.3 (1.21).

Table 3. Early postoperative outcome

Early postoperative outcome	Number of patients	Percentage
Prolonged ventilation	10	20.0%
Return to operative room	3	6.0%
30-day mortality	2	4.0%
Stroke	1	2.0%
Renal failure	2	4.0%
Post op MI	3	6.0%
Need for Inotropes	42	84%
Adrenaline	22	44.0%
Dobutrex	12	24.0%
Noradrenaline	26	52.0%
IABP	6	12.0%
Levosemindan	15	30.0%
ICU stay (hours) Mean ± SD Range	73.2 ± 15.12 48 - 96	
Hospital stay (days) Mean ± SD Range	10.3 ± 1.21 8 - 12	
Duration of inotropic support (hours) Mean ± SD Range	22.69 ± 13.3 12 - 60	

Postop MI, Postoperative myocardial infarction; IABP, intraaortic balloon counter pulsation

Finally, table 4. depicts the change in LV dimensions and function after the operation. No statistical significance was encountered when the preoperative and postoperative (predischarge) echocardiography was compared together. ESD and EDD decreased slightly from 3.6±0.62 cm, 5.75±0.59 cm preoperatively to 3.51±0.61 cm, 5.63±0.69 cm postoperatively with a p-value of 0.466 and 0.352 respectively. Similarly, EF and FS were very similar when compared together (41.8 ± 6.32 %, 20.8 ± 2.35 % preoperatively compared to 41.92 ± 7.49%, 20.85 ± 3.25% postoperatively). Again, a p-value was insignificant (0.937 and 0.929) respectively.

Table 4. comparison between left ventricular function pre- and postoperative

	Preoperative	Pre-discharge	Paired t-test	p-value
LVEF (%)	41.8 ± 6.32	41.92 ± 7.49	0.079	0.937
LVESD(cm)	3.6±0.62	3.51±0.61	0.732	0.466
LVEDD(cm)	5.75±0.59	5.63±0.69	0.935	0.352
LVFS (%)	20.8 ± 2.35	20.85 ± 3.25	0.088	0.929

LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; LVEDD, left ventricular end diastolic dimension, LVFS: left ventricular fraction shortening.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric by Kolmogorov-Smirnov tests. The comparison between two paired groups with quantitative data and parametric distribution was done by using the Paired t-test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant at the p-value < 0.05.

Discussion

There is currently a growing interest in the use of variable cardioplegic solutions for heart operations. Consequently, a number of different solutions and various methods had developed (Mitsuhiro Hachida, 1997) each cardioplegic method has its own advantages and disadvantages. All of them should be used appropriately by taking into account the characteristics of myocardial injury and the duration of ischemic time.

Surgeons, therefore, have learned to tailor their cardioplegic techniques to the individual patient and select the most appropriate approach to improve their results and decrease complications (Richard D., 2012).

Custidiol is an intracellular cardioplegic solution which contains low sodium concentration to arrest the heart in diastole by inhibiting the rapid phase of the action potential, this solution contains histidine as a buffer, ketoglutarate to improve ATP energy production during reperfusion, tryptophan to stabilize the cell membrane, and mannitol to decrease cellular edema and to act as a free radical scavenger(Gamal Z., 2014).

The well-integrated components of this solution contribute to myocardial preservation and recovery of its function. Aarsaether et al. (Aarsæther, 2009) proved that protein buffers such as histidine might be superior to bicarbonate in stabilizing intracellular pH and consequently, the recovery of postischemic biochemical and mechanical parameters. The buffering effect of histidine may be beneficial for severely injured myocardium in the dilated heart during prolonged ischemia.

The way Histidine improves myocardial preservation was suggested by Bretschneider and associates (Bretschneider HJ, 1980). Similarly, Del Nido and associates (Del Nido PJ, 1985) proved that histidine had a significant cardiac protective effect. The HTK solution contains no metabolic substrate nevertheless, it uses a high-capacity buffer system which is (histidine). The acidosis is, therefore, efficiently retarded by HTK solutions which in turn delay any increase in the cytosolic calcium ion integrity of the sarcolemmal membrane (Schmiedl A, 1990). The sarcolemmal ion pumps similarly have a low activity by low magnesium ion concentration in the HTK solution, thus, further conserving energy reserves. Lastly, because of the hypokalemic nature of the HTK solution and its low overall ion concentration, provision is made for a significantly higher buffer concentration.

Takeuchi et al. and Liu et al., in their studies, proved that the administration of a histidine-containing cardioplegia solution promotes anaerobic glycolysis and improves the recovery of high-energy phosphates and contractile function in the hypertrophied myocardium, which supports our clinical findings. Owing to these qualities and the high buffer capacity, it has been shown that one single dose of HTK is sufficient for myocardial protection up to more than 2 hours of ischemia (Takeuchi, 1995, Liu J, 2008).

Other amino acids, such as ketoglutarate and tryptophan, were used in HTK to provide an energy source. These components produce adenosine triphosphate via the alternative pathway without producing lactate in the cells. Moreover, the presence of a high histidine concentration outside the cells may also be beneficial because it facilitates Hydrogen ion removal from the cytosol by anionic carriers such as lactate during the ischemia (Ohkado A, 1994).

All these contribute to the significant protective effects of HTK solution for prolonged ischemia in the severely injured myocardium. Our study demonstrated that percent fractional shortening and ejection fraction after the ischemia did not deteriorate. In conclusion, the results of the present study suggest that the protective effect of the HTK method may be significant in patients with impaired heart function and undergoing complex cardiac surgery.

Del Nido et al. (Del Nido PJ, 1985) also demonstrated that myocardial necrosis can be minimized and the post-arrest contractile function can be better by buffering capacity in a crystalloid solution via preserving myocardial adenosine triphosphate stores.

Similarly, Hachida et al. (Hachida M, 1997) demonstrated that the promotion of anaerobic glycolysis during ischemia by HTK solution results in superior preservation of the contractile function of the heart.

Saitoh et al (Saitoh Y., 2000) proved that the preservation of HTK solution doesn't only protects the myocardium but also the coronary artery endothelium. In his experimental study with rat hearts, he found that HTK protected the coronary vasculature which can lead to improved functional cardiac recovery.

Sakata et al. (Sakata J, 1998) used the HTK solution for valve surgery and found more spontaneous defibrillation and lower requirement of inotropic drugs compared with the use of cold blood cardioplegia. Von Oppell et al. (Von Oppell U, 1990) stored cultures of human endothelial cells in different cardioplegic solutions and temperatures. According to their findings, the best available solution for hypothermic endothelial cell preservation is HTK.

The superiority of HTK solution at hypothermia appears to be due to the low chloride content of intracellular solutions and the additives histidine, tryptophan and KH-2-. Moreover, It is well known that HTK should not be given in higher temperature in clinical practice as this may result in a stone heart (Fabiano F., 2013).

Many authors compared HTK solution with blood cardioplegic solutions. Braathen et al. (Braathen B, 2011) found that a single dose of HTK solution resulted in outcomes similar to those achieved with multidose cold-blood cardioplegia for mitral valve surgery. However, the same group found that HTK did not provide as good protection as cold-blood cardioplegia for aortic valve surgery (Braathen B, 2010).

In 2006 Braathen et al **(Braathen B, 2006)** showed that the Custodiol group had better left-ventricular contraction preservation, superior mitochondrial function, and using myocardial biopsy specimens, significantly lower markers of myocardial damage than cold-blood cardioplegia.

It was found that postoperative cardiac enzyme release has been associated with diminished long-term survival (Domanski MJ, 2011)

Similarly, perioperative low cardiac output syndrome has been associated with a higher incidence of complications (Rao V, 1996). These two can occur with postoperative MI. In this study, we did not measure postoperative cardiac enzymes as a routine but only when clinically indicated (like suspicion of postoperative MI) as per hospital protocol.

In a recent systemic review, offers myocardial protection that is equivalent to that of conventional cardioplegia (blood or extracellular crystalloid). However, the body of evidence available from which we can draw conclusions is limited by the small number of randomised patients. A single dose cardioplegia strategy for myocardial protection has significant benefits for the performance of minimally invasive or complex cardiac surgery and the analysis of this recent review supported its ongoing use. However, there was not enough evidence to recommend the routine use of for the performance of coronary artery bypass grafting (CABG) or other simple open cardiac surgical procedures (James B., 2013).

Conclusion

A single dose of an HTK cardioplegic solution provides good myocardial protection in complex cardiac surgery with mild to moderate impairment of LV function and has a good immediate postoperative outcome.

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